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PRINCIPAL INVESTIGATOR: Andreas Kurtz, Ph.D.

CONTRACTING ORGANIZATION: Massachusetts General Hospital
Boston, Massachusetts 02114

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Andreas Kurtz, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Massachusetts General Hospital
Boston, Massachusetts 02114

E-Mail: MLSMITH@partners.org

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13. ABSTRACT *(Maximum 200 Words)*

Individuals with Neurofibromatosis Type 1 are haplotypic carriers of mutations in the NF1-gene. These mutations predispose all individuals to have symptoms of NF1, however, there is extreme variation about the severity of these symptoms. We proposed that other genetic factors than the NF1 gene are modifying disease severity. There is strong evidence that mitochondrial polymorphisms might contribute to this variation, and we attempt here to study the impact of these polymorphisms on the number of neurofibromas of NF1 patients. Two approaches are taken to identify mitochondrial polymorphisms in NF1: First, mitochondrial DNA from a subpopulation of NF1 patients with few neurofibroma numbers is compared with mtDNA from a subpopulation of NF1 patients with high neurofibroma numbers. About 200 Patients need to be analyzed in each group.
Second (and independently), mitochondrial DNA from a neurofibroma is compared with mitochondrial DNA from peripheral blood from the same patient. About 20 paired samples need to be analyzed.
Up to now, we have collected DNA from 45 patients for polymorphism analyses using the first approach. We have collected 10 paired DNA/peripheral blood DNA samples for the second approach. Using these 10 samples, mitochondrial DNA mutations have been found.

14. SUBJECT TERMS
Mitochondria, genetic polymorphism, neurofibromatosis, tumor, neurofibroma, genetic modifier

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Table of Contents

INTRODUCTION:

Mutations in the *Nf1* gene cause neurofibromatosis type 1 (NF1). This autosomal dominant disease is characterized by high penetrance but extremely variable expressivity. The characteristic variability implies a role for modifier genes in NF1 symptomatic. Several lines of evidence suggest that mitochondrial DNA polymorphisms might be responsible for some of the observed clinical variation in NF1.

Here, we propose to test the hypothesis that there is a correlation between severity of clinical symptoms in NF1 and the presence of functionally aberrant mitochondria. Following this hypothesis, these aberrant mitochondria should be more prominent in patients with severe disease manifestation and they should constitute a significant proportion of mitochondria in NF1 tumors.

Both assumptions will be tested in the course of this work. To test the first assumption, two subpopulations of NF1 individuals (n=200 each) will be recruited – one with a large number of neurofibromas and one with a low number of neurofibromas. DNA isolated from both groups will be analyzed for mitochondrial mutations and mutations correlated with the groups. To test the second assumption, mitochondrial DNA (mtDNA) from a tumor will be compared with mtDNA from germ line mtDNA (peripheral blood) from the same NF1-patient (n=20 patients).

Identification of mtDNA mutations and polymorphism associated with tumor development and disease severity would add understanding of the molecular causes of the disease and might make a prognosis with regard to disease severity possible.

(This work is closely coordinated with Dr. Andre Bernard at MGH. Dr. Bernard is conducting a study to identify genetic modifiers in NF1 looking at DNA-repair genes. Dr. Bernard is using the same subpopulations of NF1 individuals and recruiting efforts are being coordinated between our groups. His study is sponsored by the US AMRMC as well and this kind of cooperation has been suggested by the review board and was implemented.)

BODY:

The proposed analysis requires the collection of blood and DNA from two subpopulations of NF1 individuals (Table 1). According to our statistical prediction , 200 individuals in each group (NF1 individuals with few neurofibromas and many neurofibromas, respectively), in addition to 75 non NF1 individuals need to be recruited.

Table 1: Selection criteria for NF1 individuals.

Age	Number of Skin Neurofibromas	
	(Group 1)	(Group 2)
18-20 years old	fewer than 5	or more than 30
20-30 years old	fewer than 10	or more than 100
30-40 years old	fewer than 20	or more than 200
older than 40 years	fewer than 50	or more than 500

Approved statement of work months 1-20: Collection of blood and tumor samples from NF1 patients and normal controls. Clinical description, DNA isolation and banking.

The main effort in the first year of this study has been on setting up collaborations with clinicians to access the patients. An important consideration when studying mt-polymorphism is the ethnic matching of individuals in each group.

A major effort has been made to recruit patients in an ethnically relatively homogeneous population in Germany. To this end, Dr. Hernaiz Driever (Humboldt University Berlin, Charite, Department of child oncology) has been involved in the study. He has contacted all major NF-centers in this country with the results listed in Table 2.

Recruitment from these centers has started by October 31, 2001. Primary collaborator there is Dr. Mautner (Hamburg). The anticipated rate from his clinic alone is 10 patients per week.

Table 2: List of collaborating NF-centers and number of patients / center (Germany).

Dr. Mautner/Dr. Kluwe Laboratory for Braintumorbiology Neurosurgery University Hospital Eppendorf Martinistr. 52 20246 Hamburg	NF- Center (ca. 1500 very well characterized patients)
Dr. Burkhardt Köhler Clinical Director Children's Hospital I des Olga- Hospitals 70176 Stuttgart	Children and Adolexcents with NF (ca. 400 patients)

Dr. Jung and Dr. Maywald
Institute for Medical Genetics and
Molecular Medicine
Paul- Schallück- Str. 8
50939 Köln

NF patients and families (ca. 200 patients)

Dr. Thorsten Rosenbaum
Center for Child Health
Heinrich- Heine-University
Moorenstr. 5
40225 Düsseldorf

NF 1- clinic (ca. 50 Patients)

A second line of patient recruitment has been set up in the US. To that aim, NF-organizations, physicians and clinics have been contacted using several means (including email, advertising, mailing, flyers, see appendix). The response to these efforts was sporadic. An average of 0.5 to 1 patient per week can be anticipated from these activities.

In addition, patients from the MGH-NF clinic have been recruited at a rate of about one patient per week. An especially difficult task is the recruitment of individuals with very few neurofibromas since these patients do not frequently visit their physician. A larger number of centers needs to be contacted to obtain a sufficient sample size in this group.

Up to now, DNA from 45 NF1 individuals has been obtained in both groups. Control sample (Non-NF individuals) acquisition is complete. (Table 3).

Table 3: Number of samples in each group.

Subpopulation	Sample size (current)	Sample size (goal)
Low neurofibroma number	8	200
High neurofibroma number	37	200
Non-NF1	75	75

A protected database has been established for data reposition. This database contains contact information, clinical information, analysis results. DNA is banked in the laboratory of the collaborator Dr. Lee-Jun Wong at Georgetown University. Clinical information and mutation testing results are currently stored separately to assure unbiased (blinded) analysis.

Although the number of patients to date is relatively low compared to the number needed for the study, we are optimistic to meet the target numbers. Especially the finished recruitment setup in Germany is highly promising.

Tumor samples and peripheral blood samples from the same patients have been obtained from 9 individuals with NF1 from the MGH NF-clinic (Dr. Mia MacCollin and

Dr. Rosemary Foster). DNA from these samples was isolated and used for polymorphism analysis.

Approved statement of work months 1-22: Mitochondrial polymorphism and mutation screening of blood samples. Screening will be performed in increments of 20 samples.

The first 20 samples within the group 'large number of neurofibromas' has been screened for mtDNA mutations. The data have been included into the database.

Since the study is performed in a blinded manner no correlation can be drawn at this point between polymorphisms found in this sample and polymorphisms found in the general (control) population.

Approved statement of work months 12-24: Screening of tumor derived DNA for mitochondrial polymorphism by TTGE and sequencing. Analysis of heteroplasmy.

The matched tumor DNA/blood DNA samples are relatively easily obtainable and the required number of 20 samples will be available within the next month.

In addition, mt mutations have already been found using this type of analysis and will be published as an abstract at the AACR meeting (Appendix 1). In this analysis, 8 matched tumor (neurofibroma) / blood DNA samples were analyzed. N four of the tumor samples somatic mutations have been detected in mtDNA. This is a very high rate compared with other studies and a promising finding.

Approved statement of work months 12-24: Statistical analysis of accumulated data.

Statistical analysis of data will be performed after the proposed sample size has been obtained.

KEY RESEARCH ACCOMPLISHMENT

- 45 DNA samples from NF1 individuals obtained
- 75 DNA samples of non-NF1 samples obtained
- 20 DNA samples analyzed for mtDNA mutations
- 8 matched tumor and blood DNA samples obtained and analyzed for mtDNA polymorphisms
- mtDNA mutations detected in 4 of 8 neurofibroma (tumor) samples
- Recruitment algorithm and sample/data handling established for NF1 individuals in Germany
- Continuing patient recruitment in the US
- Database has been built.

REPORTABLE OUTCOMES

- Although this is an epidemiological long term study we could obtain results from matched tumor DNA / blood DNA samples from NF1 individuals by mt mutation analysis. These data will be published in abstract form at the AACR meeting (appendix).
- A DNA repository has been established for the NF1 subpopulations high vs. low number of neurofibromas.
- A database has been established containing clinical data on NF patients.
- A PhD graduate student (Maria Lueth) has been recruited in the laboratory of the collaborator Dr. Lee-Jun Wong (Georgetown University) for training in mtDNA polymorphism analysis (see CV in appendix)
- An MD graduate student (Melanie Hartmann) has been recruited in the laboratory of the collaborator Dr. Hernaiz Driever (Humboldt University Berlin, Germany) for clinical evaluation of NF1 individuals, sample collection and data banking (see CV in appendix).

CONCLUSIONS

This is an epidemiological long term study which compares (1) mtDNA between NF1 individuals with few and many neurofibroma, respectively, and (2) mtDNA from tumors with blood mtDNA from the same individual.

In the first aim of this study, 200 individuals in each group are required for statistically significant data analysis. To date, 45 individuals have been recruited, clinically characterized and DNA obtained and banked.

In addition, mtDNA from 75 non-NF individuals is necessary and this number has been obtained.

We have been able to increase our recruitment efforts and establish collaborations with 4 NF centers in Germany. We expect to be able to recruit individuals for the study at a rate of 10 / week through these centers.

We have also increased our recruitment results in the US, which stands now at 1-2 individuals /week, with the majority coming from the MGH NF-clinic.

In conclusion, we are optimistic to reach the anticipated sample size. I would like to emphasize that the collaborative efforts to recruit participants together with Dr. Andre Bernards have been very helpful.

Analysis of mtDNA in aim 1 will be in increments of 20. Thus far, 20 mtDNA samples have been analyzed and polymorphism have been catalogued. However, analysis of frequencies is not meaningful at this point because of the small sample size.

In the second aim of the study, a minimum of 20 matched neurofibroma (tumor) and blood DNAs from the same individual need to be analyzed. To date, 8 samples have been obtained and analyzed. 4 of the 8 tumor mtDNAs were mutated, an unexpectedly high rate. 20 more matched samples have been obtained in the last few days and will be analyzed in the near future.

So what ? If the initial assumption and our preliminary finding can be substantiated, it is likely that mitochondrial polymorphisms play a role in neurofibroma development. This would open a new direction of NF research. In addition, predictive analysis might be possible.

Proposed changes: We do not propose changes in the current statement of work. However, I want to mention that this is a long term study and will most likely continue beyond the time frame of this grant.

I also want to emphasize that my laboratory has moved since the grant was approved for funding from Georgetown University to Harvard University / MGH. Since the indirect cost rate at MGH is much higher than it was at Georgetown University, the grant suffered a significant loss in the direct cost budget (to keep the approved overall costs constant). As a consequence, there are no resources for reagents and supplies, which we currently cover from other funds. This has been a real problem for us and an adjustment would be very helpful.

REFERENCES

None.

APPENDICES

Abstract AACR meeting
Flyer
Letter to colleagues
Email to colleagues
Advertisement/Newsletter
CV Maria Lueth
CV Melanie Hartmann

(ABSTRACT AACR)

Somatic Mitochondria Mutations are found in Neurofibromatosis Type 1

Maria Lueth, Rosemary Foster, Andreas Kurtz, Lee- Jun C. Wong

Neurofibromatosis type 1 (NF1) with an incidence of 1 in 3500 persons is the most common inherited disease which predisposes to tumor formation. Although all individuals who carry a mutation in the *NF1 gene* also show symptoms of the disease , the severity of these symptoms varies widely among individuals. Some NF1 patients have only pigmental abnormalities whereas others have hundreds of neurofibromas and other tumors. The reason for this variability is not known.

Somatic mtDNA mutations have been reported in colorectal , bladder , head and neck , lung , and ovarian cancers.

Most of the mutations occur in D-loop region , where the origin of replication and promoters are located.

In this report we investigate the role of mitochondria of tumorgenesis of NF1 and the association between mitochondrial DNA (mtDNA) mutations and the expressivity in NF1 patients.

Thus far the entire D-loop region has been sequenced for 7 tumor pairs . In 4 of these 7 individuals (57.1%) somatic mutations were found. 3 mutations are homoplasmic or heteroplasmic insertions or deletions in np 303 – 309 poly C tract. Previous studies have shown the presence of this mutation in 4 of 19 (21%) of breast cancer samples (not published) .Our results show a frequency for this mutation of 3 in 7 (42.8 %) in NF1 samples. The high frequency of this mutation in NF1 may suggest the presence of microsatellite instability (MSI) in other repeat regions that we are currently investigating.

One of the somatic mutations is a homoplastic substitution of T16304C.

The results by sequencing were consistent with our results shown by temporal temperature gel electrophoresis (TTGE) method for 3 of these 4 mutations.

In addition numerous germline mtDNA variations were found by sequencing and the allele specific oligonucleotide (ASO) method.

Screening of 38 mtDNA variation in NF1 patients has reviewed that some of these variations may indeed associate with tumor risk.

Most significantly the T4216C substitution , which was found in 7 out of 16 patients , demonstrates that the mtDNA variations may be a modifier of tumorexpression.

(FLYER)

Title of study: Mitochondrial polymorphism and number of neurofibromas in NF1.
PI: Andreas Kurtz, PhD

We are conducting a long term research study that is designed to explore why some individuals with NF-1 develop a large number of neurofibromas whereas others develop a smaller number. We believe that there may be genes aside from the NF gene itself that determine the actual number of neurofibromas a person with NF will develop. Candidate genes might belong to mitochondria, small particles in every cell of the body.

In order to find these genes, we are recruiting individuals with NF to participate in our study. Specifically, we are looking for individuals who fit in any of the following categories:

Age	Number of Skin Neurofibromas
18-20 years old	fewer than 5 or more than 30
20-30 years old	fewer than 10 or more than 100
30-40 years old	fewer than 20 or more than 200
older than 40 years	fewer than 50 or more than 500

If you fit into any of the above categories and are interested in participating, or have any questions, please contact the investigator in charge of this study (contact information below). After this initial contact, participants will need to visit their regular physician to donate 20 ml of blood (about 4 teaspoons). The physician will also conduct a brief physical examination to estimate the number of neurofibromas.

Contact information:

Andreas Kurtz, Ph.D.
Phone: (617) 726-5620 Fax: (617) 726 5677
e-mail: kurtza@helix.mgh.harvard.edu

Massachusetts General Hospital
Boston, Massachusetts

(LETTER)

MASSACHUSETTS GENERAL HOSPITAL – HARVARD MEDICAL SCHOOL

THE MGH CANCER CENTER

Building 149 13th Street, Charlestown MA 02129-2000
Telephone: 617-724 2953 (lab) 726-4821 (office & voicemail) FAX: 617-724-9610
email: kurtza@helix.mgh.harvard.edu

Molecular Neurosurgery Laboratory
Andreas Kurtz Ph. D.
Assistant Professor for Neurosurgery (Genetics)

May 29, 2000

[Click **here** and type recipient's address]

Dear Colleague:

We are conducting a genetic study to determine whether polymorphism in mitochondrial genes affect the rate of neurofibroma formation in neurofibromatosis type 1 (NF1) subjects. To test this hypothesis we will determine frequencies of known mitochondrial polymorphism in NF1 subjects that either show higher or lower than expected neurofibroma numbers. For the purpose of this study we define high neurofibroma subjects primarily as those in the 15 to 20 year age group with more than 30 neurofibromas, 20-30 year old subjects with >100, or 30 to 40 year old subjects with >200 tumors. Similarly, low neurofibroma subjects are those that have fewer than 5, 10 or 20 tumors in the 15-20, 20-30, and 30-40 year age ranges.

If you have subjects that match the above criteria and who may be interested in participating in this study, please contact me at (617) 726-4821, or at kurtza@helix.mgh.harvard.edu Thank you very much for your attention to this matter.

Sincerely,

Andreas Kurtz, Ph.D.

(EMAIL)

MASSACHUSETTS GENERAL HOSPITAL – HARVARD MEDICAL SCHOOL

THE MGH CANCER CENTER

Building 149 13th Street, Charlestown MA 02129-2000
Telephone: 617-724-2953 (lab) 726-4821 (office & voicemail) FAX: 617-724-9610
email: abernard@helix.mgh.harvard.edu

Molecular Neurosurgery Laboratory
Andreas Kurtz, Ph. D.
Assistant Professor of Neurosurgery (Genetics)

Draft email to NNFF mailing list clinicians

Dear Colleague:

We are conducting a genetic study to determine whether alleles of DNA repair or cell cycle checkpoint (a.k.a. caretaker) genes and / or polymorphic mitochondria affect the rate of neurofibroma formation in NF1 patients. To test this hypothesis we will determine allele frequencies of a comprehensive set of DNA repair and cell cycle checkpoint and mitochondrial genes in NF1 subjects that either show higher or lower than expected numbers of neurofibromas. For the purpose of this study we define high neurofibroma subjects primarily as those in the 15 to 20 year age group with more than 30 neurofibromas, 20-30 year old subjects with >100, or 30 to 40 year old subjects with >200 tumors. Similarly, low neurofibroma subjects are those that have fewer than 5, 10 or 20 tumors in the 15-20, 20-30, and 30-40 year age ranges.

If you have subjects that (roughly) match the above criteria and who might be interested in participating in this study, please contact me at (617) 726-4821, or at kurtza@helix.mgh.harvard.edu. You might also contact Dr. Andre Bernards at (617) 726 5680 or at abernard@helix.mgh.harvard.edu Thank you very much for your attention to this matter.

Sincerely,

Andreas Kurtz

(NEWSLETTER)

Modifier of neurofibroma formation in NF1 – call for participants

Neurofibromatosis type 1 (NF1) is a common autosomal dominantly inherited disease caused by mutations in the *Nf1* gene. Although penetrance of NF1 is 100% the severity of clinical symptoms varies widely, even between members of the same family and between patients bearing the same mutation within the *Nf1* gene. The reason for this variability is not understood and genetic as well epigenetic modifiers are possible causes. A number of studies on the effects of hormonal, environmental, and genetic influences in NF1 were initiated, but to date, neither non-genetic nor genetic factors were determined which completely explain this variability.

However, previous studies have provided strong evidence that genetic factors are indeed the background for clinical variation in NF1 (Easton, Huson and Hughes, Riccardi), and this has been substantiated by studies performed on animal models of NF1.

Knowledge of NF1 modifiers might allow a prediction of disease severity, which would be of great benefit for NF1 patients and their relatives. Here we set out to identify modifiers for the numbers of neurofibromas in NF1 individuals. The study focuses on two large groups of genes.

The first group concerns genes which are involved in cell cycle control. It is conceivable that individual modifications in these genes can result in a variable growth rate of tumors. The second group concerns genes in mitochondria. Mitochondria are organelles within each cell of the body. They are responsible for energy production and important regulators for DNA damage and apoptosis. Modifications in mitochondria are maternally inherited, but they can also arise somatically, leading to mosaic distribution patterns of a phenotype. Furthermore, they can enhance cell viability and tumor growth.

In addition to screen cell cycle checkpoint- and mitochondrial genes for polymorphism, the study will establish a platform to identify other genes that might affect the rate of neurofibroma development in NF1. The project also has broader implications, since any gene that accelerates neurofibroma formation is also likely to increase overall cancer risk.

To perform this long term study we call for the participation of NF1 individuals. Specifically, we call for individuals with NF-1 who develop a large number of neurofibromas or who develop a small number of neurofibromas. We are looking for individuals who fit in any of the following categories:

Age	Number of Skin Neurofibromas
18-20 years old	fewer than 5 or more than 30
20-30 years old	fewer than 10 or more than 100
30-40 years old	fewer than 20 or more than 200
older than 40 years	fewer than 50 or more than 500

If you are interested in participating, or have any questions, please contact the investigators in charge of this study, Dr. Andrea Bernard and Dr. Andreas Kurtz (contact information below). After this initial contact, participants will need to visit their regular

physician to donate 20 ml of blood (about 4 teaspoons). The physician will also conduct a brief physical examination to estimate the number of neurofibromas.

Contact information:

Andreas Kurtz, Ph.D.
Phone: (617) 726-5620
Fax: (617) 726 5677
e-mail: kurtza@helix.mgh.harvard.edu

Andre Bernard
Phone: (617)726 5620
fax: (617)724 9648
email: abernard@helix.mgh.harvard.edu

Massachusetts General Hospital
Boston, Massachusetts

Curriculum Vitae

Name:	Maria Lueth, MD
PII Redacted	
[redacted]	[redacted]
Current Position:	Postdoctoral fellow, Georgetown University
[redacted]	[redacted]
[redacted]	[redacted]
Education:	1990-1995 High school; Rostock 1995: College Board Exam 1995-2000 : Medical School at Humboldt-University; Berlin 2001-present : Postdoctoral fellow at department of molecular Gernetics, Georgetown University , Washington DC
Qualifications:	Physikum 1. State Examination (MD)

PII Redacted

(CV MELANIE HARTMANN)

Melanie Hartmann, MD, [redacted], Tel./Fax: 030/3233286, EMail: Hartmann.Melanie@web.de

Curriculum Vitae

[redacted] [redacted]

Current Position:	Research Student (Physician in Practice) at Department of Child Oncology, Humboldt University Berlin Project: Mitochondrial polymorphism in NF1
Education/Qualification:	1989-1992 Highschool specialization biology and nutrition 1992-1994 Qualification to medical-technical laboratory assistant at Dr. Gillmeister School, Heide 1/1995-3/1995 Technician at the Hormone- and Tumormarkerlab, University Hospital Hamburg Eppendorf 11/1995-2000 Part time technician at the central laboratory Charité Campus 1995-2000 Medical School Charite, Humboldt University Berlin (MD)
Dissertation:	Dr. O. Sezer / Prof. K. Possinger Medical Clinic / Oncology und Hematology Charité Campus Mitte Topic: Apoptoseinduction by Anthracyclinderivates in human Myelom cells
Congresses:	06.05. -09.05.1998 Congress of Molecular Medicine in ICC Berlin (Abstract/Poster) 25.- 28.10.1998 Abstract/Poster Annual Congress of the German and Austrian Societies of Haematology and Oncology 22.04. -23.04.1999 Workshop „Apoptose in Tumor Research“ Friedrich-Schiller-University Jena 25.07.1999 Dermato-surgical course at HU-Berlin
Languages:	English and „Medical English“ French